

BEST AVAILABLE COPY

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : A61K 9/127, 9/107, 9/06</p>	<p>A1</p>	<p>(11) International Publication Number: WO 94/03157</p> <p>(43) International Publication Date: 17 February 1994 (17.02.94)</p>		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> <p>(21) International Application Number: PCT/EP93/01965</p> <p>(22) International Filing Date: 23 July 1993 (23.07.93)</p> <p>(30) Priority data: MI92A001831 28 July 1992 (28.07.92) IT</p> <p>(71) Applicant (for all designated States except US): POLI INDUSTRIA CHIMICA S.P.A. [IT/IT]; Piazza Agrippa, 1, I-20141 Milano (IT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): POLI, Stefano [IT/IT]; MAILLAND, Federico [IT/IT]; MORO, Luigi [IT/IT]; Via Volturmo, 48, I-20089 Quinto de' Stampi-Rozzano (IT).</p> <p>(74) Agent: BIANCHETTI, Giuseppe; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).</p> </td> <td style="width: 50%; border: none; vertical-align: top;"> <p>(81) Designated States: CA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> </td> </tr> </table>			<p>(21) International Application Number: PCT/EP93/01965</p> <p>(22) International Filing Date: 23 July 1993 (23.07.93)</p> <p>(30) Priority data: MI92A001831 28 July 1992 (28.07.92) IT</p> <p>(71) Applicant (for all designated States except US): POLI INDUSTRIA CHIMICA S.P.A. [IT/IT]; Piazza Agrippa, 1, I-20141 Milano (IT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): POLI, Stefano [IT/IT]; MAILLAND, Federico [IT/IT]; MORO, Luigi [IT/IT]; Via Volturmo, 48, I-20089 Quinto de' Stampi-Rozzano (IT).</p> <p>(74) Agent: BIANCHETTI, Giuseppe; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).</p>	<p>(81) Designated States: CA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(21) International Application Number: PCT/EP93/01965</p> <p>(22) International Filing Date: 23 July 1993 (23.07.93)</p> <p>(30) Priority data: MI92A001831 28 July 1992 (28.07.92) IT</p> <p>(71) Applicant (for all designated States except US): POLI INDUSTRIA CHIMICA S.P.A. [IT/IT]; Piazza Agrippa, 1, I-20141 Milano (IT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): POLI, Stefano [IT/IT]; MAILLAND, Federico [IT/IT]; MORO, Luigi [IT/IT]; Via Volturmo, 48, I-20089 Quinto de' Stampi-Rozzano (IT).</p> <p>(74) Agent: BIANCHETTI, Giuseppe; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).</p>	<p>(81) Designated States: CA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>			
<p>(54) Title: PHARMACEUTICAL COMPOSITIONS FOR TRANSMUCOSAL DELIVERY OF PEPTIDES</p> <p>(57) Abstract</p> <p>Bioadhesive microemulsions or liposomic dispersions containing proteic substances, especially calcitonin, that allow the systemic, local or topical administration of drugs by transmucosal route are described. This type of administration shows some considerable advantages of activity, tolerability, dosage individualization and drug stability.</p>				

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

PHARMACEUTICAL COMPOSITIONS FOR TRANSMUCOSAL DELIVERY OF PEPTIDES.

The present invention refers to pharmaceutical compositions in the form of microemulsions or liposomic dispersions for the transmucosal administration of proteins or peptidic substances pharmacologically active; they differ from the known liposomic or microemulsified compositions in that they contain in addition a thermosetting agent able to enhance the residence time on the administration site and, consequently, to promote the absorption of the delivered drug.

The administration of proteinic substances has been, from few years ago, limited to the parenteral route as it was the only one which granted a good absorption to molecules having a complex structure and not able to tolerate environments with a high acidity and rich of proteolytic enzymes such as that ones can be found in the digestive apparatus. The need to apply by means of an invasive way, the difficulty in obtaining, on a large scale, many proteins from natural sources and the very high activity of such substances, with the consequent risks of overdosage, have determined the limited diffusion of such substances in the clinical practice.

Recent attempts to orally administer the peptide substances with drug delivery systems such as microparticles and liposomes, did not obtain relevant

results in absorption or reproducibility of the same:
the transit time variability in the digestive
apparatus, associated to the large presence of
proteolytic enzymes, has made the researcher to
5 consider the oral administration as a problem.

More recently, always in the attempt to avoid the
more invasive parenteral administration, formulations
suitable to the nasal administration of proteinic
substances have been proposed.

10 The typical disadvantage of this way of
administration consists in: the relatively reduced area
available for the absorption, the high clearance (which
reduce the time of contact) and the particular
characteristic of the muconasal epithelium which covers
15 the upper respiratory organs, that is the presence of
cilia in association with mucus producing glands.

In addition, the "absorption promoters" frequently
used in formulations for nasal administration produce a
relevant damage to the mucociliary clearance of the
20 deposit zone of the formulation and give problems to
the repeated or chronic treatment cycles.

With the same aims, it has also been proposed the
rectal administration of protein substances: this kind
of administration is nevertheless confined in the
25 mediterranean area and even considered unproposable to
the nordamerican and nordeuropean populations. In
addition to the ethnical inconvenient, is to be
considered that the rectal ampoul has a limited surface
and a basic pH.

30 More recently it has been found that the
intravaginal way, till now considered for local

treatment only, can be used to allow the systemic absorption of protein substances. The vaginal mucous is in fact able to allow the diffusion of substances pharmacologically active from the application surface to the dermic stratum where is present a rich vascular area able to absorb and drain in the systemic circle, besides the deep dermic stratum, considerable quantity of the substance applied.

An important characteristic which allow high absorption values in the vaginal area, as well as for nasal cavity and mucous in general, is the bioadhesion of the formulation.

The formulations commonly used in the medical practice take advantage of the vehicle characteristics: its viscosity and composition play an important role on the time of persistence of the drug effective amount in the absorption area, as well as the achievement of an opportune absorption area and the extension of the same.

Generally, the lower is the mobility of the vehicle, the higher is its viscosity then, the more permanence time increases, consequently, higher is the possibility that active substance is quantitatively absorbed.

Nevertheless, we must not neglect the fact that, usually, a reduced viscosity helps to spread the dispersion of the dosage applied by means of suitable mechanical devices, such as the nasal minipump or foam generators, allowing a very fine distribution of the product. This is very important to increase the contact surface and promote drug absorption.

The objects of present invention are pharmaceutical compositions in the form of microemulsions or liposomic dispersions characterized by the fact that contain a thermosetting agent able to
5 allow the product viscosity increase with temperature, thus allowing a longer mucousal residence time and enhanced drug absorption profile.

Due to the thermosetting properties of the vehicles it is possible to make pharmaceutical
10 compositions which have a reduced viscosity at room temperature, helping the distribution on a larger surface, with a product finely divided. When the composition reach the mucous a structural change take place as a function of the body temperature, the
15 viscosity of the product increase thus determining a large persistence of the system on the absorption zone.

The use of formulations that are liquid at room temperature but which increase their viscosity with temperature giving semi-solid products when warmed to
20 the body value is already known.

There are, in fact, some patents that describe the use of a particular polymer (Pluronic) to reach that goal.

As example, the U.S. Pat. No. 4,478,822 describes
25 a vehicle useful to deliver a medicament to a body orifice, with a drug delivery system consisting of a clear liquid which forms semi-solid gel at human body temperature.

The desired sol-gel transition temperature of the
30 solution can be modified by changes in polymer concentration or in chemical characteristics of the

solution.

We have surprisingly found that the same goal can be obtained also in systems more and more complex, like liposomes of microemulsions.

5 Normally, this type of formulations require an hard work to balance the composition. In fact, microemulsions are a very complex system with the coexistence of at least three different phases: a disperse phase, an interface layer of surfactants and/or cosurfactants surrounding the disperse phase, a
10 continuous phase that contains the previous ones. The addition of relevant amounts of copolymer in order to obtain the sol-gel system transition, normally change dramatically the precise ratio between the 4 main
15 components of the microemulsion system, that are water, surfactants, cosurfactants and oil. Only a formulation work devoted to find a new balance point allows to obtain thermosetting microemulsions. The same problem, with due proportions and limitations, is arising also
20 to liposomic dispersion.

In a typical realization, the invention uses as thermosetting vehicle, a polyoxyethylene-polyoxypropylene copolymer, preferably the one known with the trade name of Pluronic F 127TM or Lutrol F 127TM. These
25 characteristics, which are favourable even when present in conventional solutions, are particularly important and effective when join complex and modern vehicles such as the liposomic or microemulsion systems.

The liposomic systems, well-known for their
30 potential of vectorization, consist in spherules, with very small dimensions, composed of concentric layers of

phospholipidic material which are alternated to discrete and isolated aqueous spaces.

The high affinity with mucouses, typical of liposomic systems, is dramatically increased by the introduction of thermosetting polymers, generating a product with bioadhesive characteristics which, by increasing the potential of vectorisation, leads to an improved activity.

For the liposomic products, that contain the polyoxyethylene-polyoxypropylene copolymer, the viscosity changement induced by the temperature is reversible (fig. 1).

What previously said can be extended to the microemulsioned systems too: the well proportioned combination of its constituent, essential from a structural point of view, with a polyoxyethylene-polyoxypropylene copolymer produces an "apparent solution" able to increase the viscosity when in contact with mucouses. The human body application of this system, following the partial solvent evaporation, generates a barrier which, owing to the thermosetting gelation, promotes the bioadhesion of the system.

Even in this case the transition temperature from the sol condition to the gel is reversible (fig. 2).

Object of the present invention are pharmaceutical compositions useful for the transmucousal administration, in particular vaginal or nasal, of proteinic or peptidic substances pharmacologically active. Examples of similar substances include calcitonin, insulin, desmopressine, interleukin, irterferon, GMCSF (granulocyte monocyte colony

stimulating factor), ciclosporin, posatirelin, protirelin, timopentin, pidotimod, mono or polyclonales antigenes, antigenic proteins of bacterial or viral origin, parathormon, gonadorelin, coagulation factors, 5 epidermic growth factors, "insulin like" growth factor, endorphin and their derivatives or fragments, tioxoprollylcysteine, tioxoprollylthiazolidincarboxylic acid, irudine and their derivatives.

10 The pharmaceutical compositions, in accordance to the invention, can be in any form suitable for vaginal or nasal administration, such as soft gelatine vaginal capsules, vaginal suppository composed of natural or semi-synthetic glycerides, creams, gels, emulsions, suspensions, solutions, foams.

15 The liposomic systems can contain:

- modulators of transition temperature of phospholipids, such as cholesterol and its derivatives;
- antioxidant agents such as tochopherols, and their 20 esters, BHA, BHT, carotenes;
- stabilizer agents;
- preservatives;
- an alcoholic solvent phase;
- eventual auxiliary substances, such as pH 25 correctors, moisturizers, perfumes, essences.

The microemulsion systems, in addition to the components already mentioned and to the polyoxyethylene-polyoxypropylene copolymer, could contain excipients known by the experts with the names 30 of antioxidant, stabilizer, preservatives, buffers, and so on.

Obviously, the administration of liposomic and microemulsions systems will be made easier by the use of suitable spray dispensers or applicators in form of cannula, syringe or similar devices.

5 According to a preferred embodiment of the invention, the compositions will contain stabilizer or absorption promoter, polygalacturonic acid, polyglucuronic acid, hyaluronic acid, hyaluronamine, hyaluronamide or their salts and pharmaceutical
10 acceptable derivatives.

 In vivo experimental studies employing products relevant to the invention, have shown that intravaginal or nasal route allow a systemic bioavailability comparable with that ones achievable by a parenteral
15 administration, without presenting the limits of this route. As a consequence the dosage potency of proteins or peptidic substances pharmacologically active by vaginal or nasal administration will be substantially
20 similar to those already used for the well-known administration routes. It is possible that, using pharmaceutical forms not exactly metered, such as solutions, creams or gel, according to the invention, it is possible to obtain a personalization of the
25 dosage: considering the often high pharmacological activity of the protein substances, this gives important advantages related to the reduction of the risks of overdose.

 According to a preferred embodiment, the invention gives pharmaceutical compositions suitable to the
30 vaginal or nasal administration containing as active ingredient a calcitonin of any source.

The high bioavailability level achievable by the vaginal administration of a calcitonin products relevant to the invention, with a proper bioadhesion, is shown by a pharmacological experiment. The decrease of calcemic level in rabbit serum after vaginal application of: a) a simple solution, b) a thermosetting gel and c) a thermosetting gel furtherly thickened with hyaluronic acid, has been measured. As a reference the decrease of calcemic serum level obtained by administration of an equal dose of the same drug by i.m. route (see tab. 1) was chosen.

Table 1

ADMINISTRATION		CALCEMIC LEVEL VS BASAL VALUE	
TYPE	ROUTE	AREA (cm ²)	% VS I.M.
Solution 100 I.U.	i.m.	444	100
Solution 100 I.U.	vaginal	264	60
Gel(Pluronic FL27) 100 I.U.	vaginal	439	99
Gel(High m.w. Hyalur.Acid)100 I.U.	vaginal	425	95

The demonstration of a systemic absorption of proteic substances, when administrated by vaginal or nasal route employing liposomic or microemulsions bioadhesive preparations, make possible a vaccine-therapy uninvative or other forms of immunitary protection using antigen substances.

It is well-known that the oral administration of drugs meets the compliance of patients; but it is well-

known too that a simple pharmaceutical oral dosage form cannot be employed with peptides or proteins. The object of the present invention is a pathway to bypass the limits of the oral route keeping a good compliance of the patients.

Nevertheless the thermosetting liposomes or microemulsions not only are a drug delivery system particularly usefull for peptides and proteins, but can be advantageously employed also for low molecular weight drug, like nicotine, FANS and so on.

The invention will have a more detailed description by the following examples.

Example 1

Lecithin (4 g), and cholesterol (0.75 g) were dissolved in ethyl alcohol. Tocopherol acetate (0.02 g) was added to the solution. In an other container, sodium methylparaben (0.15 g), edetate disodium (0.1 g) and salmon calcitonin (7 mg) were dissolved in purified water (80 mL). The aqueous solution was added to the first one under stirring. The alcohol was evaporated by heating to form a liposomic dispersion . Thereto were added Lutrol F127 (13 g) and purified water (q.s.to reach 100 mL). The liposomic dispersion was subdivided in glass vials that following were closed with a minipump. A pre-arranged unit dose administration was so allowed.

Example 2

Soybean lecithin (30 g), tocopherol acetate (500 mg) and cholesterol (2 g) were dissolved by heating in isopropyl alcohol. The solution was kepted at 50°C until 50 mM citrate buffer (pH 4.5, 1000 mL) containing

calcitonin (50 I.U./mL), beforehand heated at the same temperature, was added, to give a hydro-alcoholic phospholipid dispersion. The mixture was vigorously shaken under reduced pressure causing the evaporation of isopropyl alcohol and giving a liposomic dispersion of calcitonin. Hydroxyethylcellulose (10 g) was added and a gel, having a suitable viscosity for the vaginal application, was obtained.

Example 3

Hyaluronic acid sodium salt (10 g) and Posatirelin (3.33 g) were dissolved in 50 mM citrate buffer (pH 4.5, 1000 mL). A suitable amount of Pluronic F127 was added, so to obtain an increased viscosity to body temperature. The gel formed shows a good clearness and can be applied into the vagina syringe dispenser.

Example 4

Lecithin (6 g) was dissolved in a mixture of isopropyl myristate and ethyl alcohol (12.5 mL). After complete dissolution tocopherol acetate (0.02 g) was added. Thereto sodium cholate (4 g) was suspended. Into an other container sodium methylparaben (0.15 g) and calcitonin (7 mg) were dissolved in purified water (60 mL). Aqueous solution of calcitonin was added to lipophylic phase, maintained vigorously shaken. To the formed microemulsion, Pluronic F127 (15 g) was added and dissolved. A necessary amount of purified water to make the entire amount 100 mL was added. The microemulsion was optically clearless and shown a transition temperature sol-gel of about 30-40°C.

Example 5

Edetate disodium (0.15 g), sodium methylparaben

(0.225 g) and salmon calcitonin (12 mg) were dissolved in purified water (100 mL). A solution, obtained dissolving lecithin (5.6 g), cholesterol (1.12 g) and tocopherol in slightest amount needed of ethyl alcohol, was added. Thereto polyoxyethylene-polyoxypropylene copolymer (Pluronic F127, 19.5 g) was dissolved, and a necessary amount of purified water to make the entire amount 150 mL was added. The liposomic dispersion was subdivided into aerosol pressurized container giving a thermosetting liposomic foam.

Example 6

Lecithin (30 g) and nicotine (3.8 g) were dissolved in a mixture of isopropylmyristate and ethyl alcohol, keeping at 50°C until dissolution. After complete dissolution tocopherol acetate (0.6 g) was added and sodium cholate (15 g) was suspended. Into an other container sodium methylparaben (0.5 g) and sodium edetate (0.5 g) were dissolved in pre-heated (60°C) purified water (300 mL). Aqueous solution was added to lipophilic phase, maintained vigorously shaken. The formed microemulsion was cooled to 5-10°C then Pluronic F127 (75 g) was added and dissolved. A necessary amount of purified water to make the entire amount 500 mL was added. The microemulsion, that shown a transition temperature sol-gel of about 30-40°C, can be applied on the skin or on the nasal mucousal with a suitable device.

CLAIMS

1. Pharmaceutical compositions suitable to drug
protein or peptide administration on body mucosal
5 surface characterized in that they are composed by:
 - a) a multiphasic pharmaceutical administration system
containing the active drug substance;
 - b) a thermosetting polymer or copolymer able to
enhance the viscosity of the system after the
10 exposition to the body temperature;
2. Pharmaceutical compositions as described in the
claim 1, characterized in that the multiphasic
pharmaceutical administration system is represented by
a liposomic suspension or dispersion.
- 15 3. Pharmaceutical composition as described in the
claim 1, characterized in that the multiphasic
pharmaceutical administration system is represented by
a microemulsion or other pluriphase system containing
at least a dispersed oily phase and a continuous
20 aqueous phase or a dispersed aqueous phase and a
continuous oily phase.
4. Pharmaceutical compositions as defined in the
preceeding claims, characterized in that these are
suitable to promote protein or peptide drugs absorption
25 through the skin or mucousal membranes.
5. Pharmaceutical compositions as defined in the
preceeding claims, characterized in that these are
suitable to promote protein or peptide drugs absorption
through the vaginal mucousal tissue.
- 30 6. Pharmaceutical compositions as defined in the
preceeding claims, characterized in that these are

suitable to promote protein or peptide drugs absorption through the nasal mucousal tissue.

7. Pharmaceutical compositions as defined in the preceeding claims, characterized in that these are
5 suitable to promote protein or peptide drugs absorption through the rectal mucousal tissue.

8. Pharmaceutical compositions as specified in the preceeding claims, characterized by the presence of polyoxyethylene-polyoxypropylene copolymers as thermo-
10 setting agents (able to increase the product viscosity by mean of the sol-gel phase transition induced by the exposition to the temperature of the body administration site).

9. Pharmaceutical compositions according to claim 8,
15 where the thermosetting agent is represented by a copolymer known with the trade name of PLURONIC F127TM, in a final concentration range between 10% and 30% w/w, preferentially between 13% and 20% w/w.

10. Pharmaceutical composition according to the preceeding claims, containing a protein or peptide drug
20 selected from the group consisting of calcitonin, insulin, desmopressine, interleukin, interferon, GMCSF (granulocyte monocyte colony stimulating factor), ciclosporin, posatirelin, protirelin, timopentin, mono
25 or polyclonal antigens, bacterial or viral antigenic protein, parathormon, gonadorelin, coagulation factors, epidermic growth factors, "insuline like" growth factor, endorphin and derivatives or fragment, thioxopropylcysteine, thioxoprolilthiazolidincarboxylic
30 acid, nicotine, irudine and/or their derivatives.

11. Pharmaceutical compositions according to the

preceeding claims, where the protein or peptide drug is represented by a calcitonin.

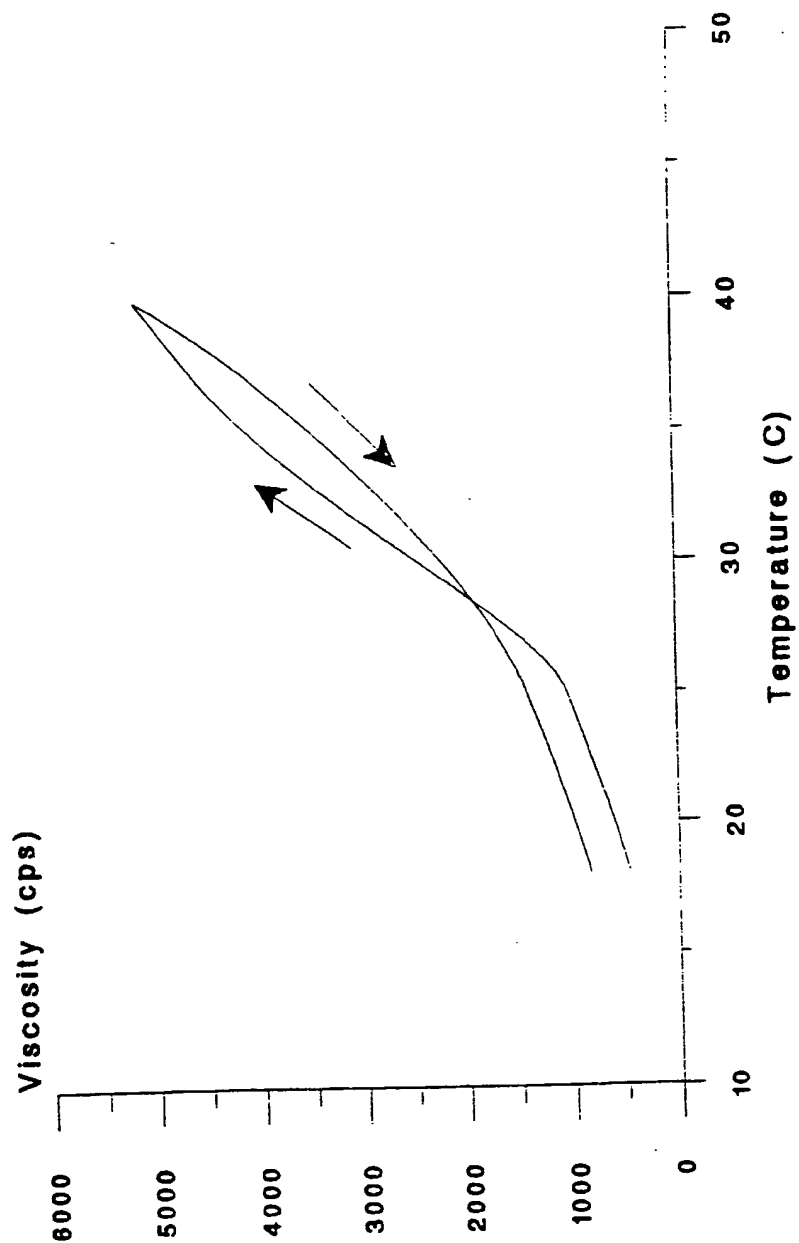
12. Pharmaceutical composition according to the preceeding claims, where the drug is represented by an antigen or an antibody suitable to be used for immunotherapy.

13. Pharmaceutical compositions according to the preceeding claims, containing as absorption enhancers or stabilizers one or more of the biopolymers polygalacturonic acid, polyglycuronic acid, hyaluronic acid, hyaluronamide or their salts or derivatives.

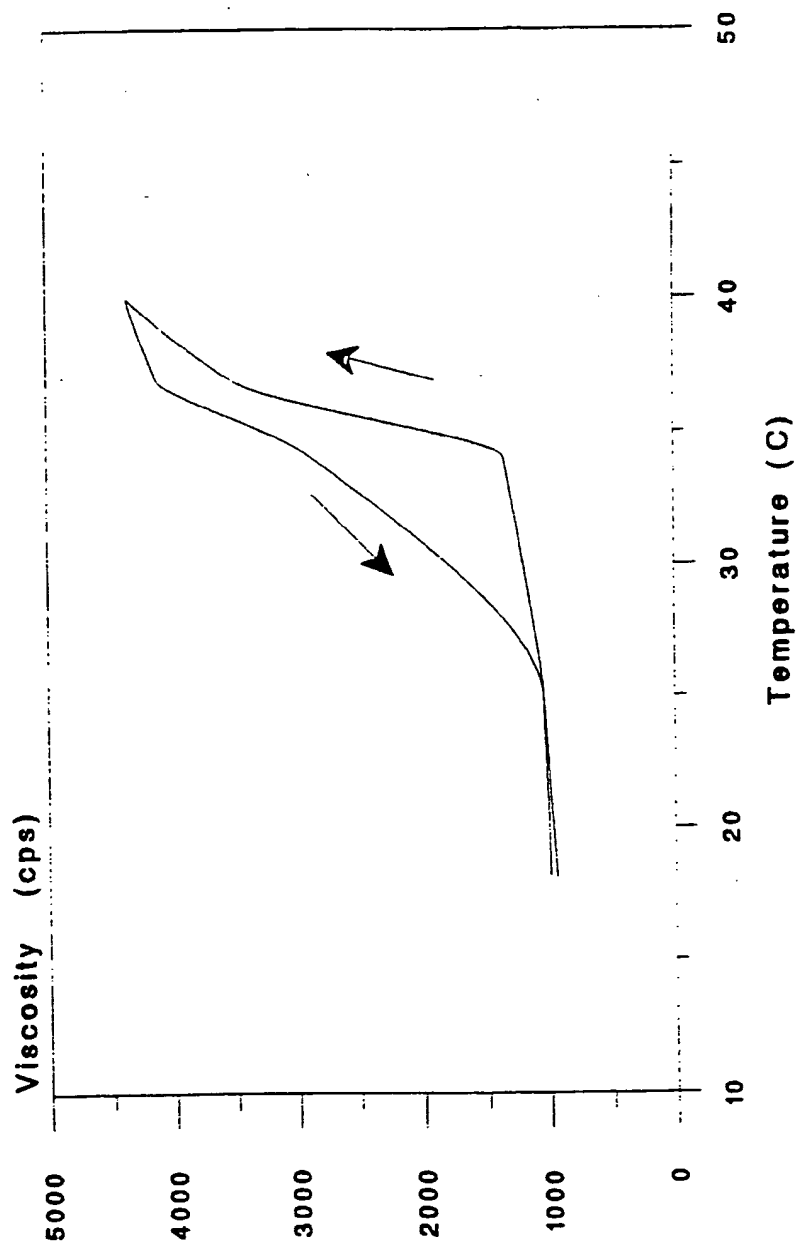
14. Pharmaceutical compositions according to the preceeding claims able to be administered as dermal or vaginal foam.

1/2

THERMOSETTING LIPOSOMES - Figure 1



2/2

THERMOSETTING MICROEMULSIONS - Figure 2

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/EP 93/01965

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/127 A61K9/107 A61K9/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,90 00048 (TEMPLE UNIVERSITY OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION) 11 January 1990 see page 1, line 17 - line 26 see page 3, line 9 - line 10 see page 5, line 15 - line 25 see page 8, line 25 - page 9, line 29 see page 12 - page 14; example 1 ---	1
Y	EP,A,0 386 960 (AMERICAN CYANAMID COMPANY) 12 September 1990 see page 1, line 1 - page 5, line 35 see page 7, line 36 - page 8, line 20 ---	1-14
Y	US,A,4 944 948 (USTER ET AL) 31 July 1990 see the whole document ---	1,2,4-14
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

4 January 1994

Date of mailing of the international search report

14. 01. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

Int: onal Application No
PCT/EP 93/01965

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 177 223 (MEZEI) 9 April 1986 see page 4, line 21 - page 5, line 8 see page 5, line 27 - line 30 see page 7, line 6 - line 17 see page 8, line 24 - page 11, line 13 -----	1-14
X	FR,A,2 660 192 (POLI INDUSTRIA CHIMICA S.P.A.) 4 October 1991 see page 8 - page 9; example 8 -----	1,2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 93/01965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9000048	11-01-90	US-A- 4917892	17-04-90
		AU-B- 613298	25-07-91
		AU-A- 3851889	23-01-90
		EP-A- 0393164	24-10-90
		JP-T- 3501485	04-04-91
EP-A-0386960	12-09-90	GB-A- 2229443	26-09-90
		AU-B- 632539	07-01-93
		AU-A- 5076990	20-09-90
		JP-A- 2300114	12-12-90
US-A-4944948	31-07-90	AU-A- 5182590	26-09-90
		EP-A- 0460100	11-12-91
		WO-A- 9009782	07-09-90
		US-A- 5064655	12-11-91
EP-A-0177223	09-04-86	JP-A- 61085312	30-04-86
		US-A- 4897269	30-01-90
		US-A- 4761288	02-08-88
FR-A-2660192	04-10-91	DE-A- 4110779	02-10-91